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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
William J. BOLOGNA et al.

Confirmation No.: 1022

Patent No.: 6,818,672 B1

Application No.: 10/089,796

Patent Date: November 16, 2004

Filing Date: July 24, 2002

For: TREATING ENDOMETRIOSIS OR INFERTILITY, OR IMPROVING FERTILITY

Attorney Docket No.: 801505-2199

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. § 1.322

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Patentees hereby respectfully request the issuance of a Certificate of Correction in connection with the above-identified patent. The corrections are listed on the attached Form PTO-1050, submitted in duplicate. The corrections requested are as follows:

At column 3, line 39, delete "Levine, et. al.," and insert -- Levine, et al., --.

At column 5, line 48, delete "fuirther" and insert -- further --; and at line 55, delete "water-insoluble. water-swellable," and insert -- water-insoluble, water-swellable --.

At column 6, line 42, delete "Convention. Inc.," and insert -- Convention, Inc., --.

At column 9, line 4, delete "(50¯C)" and insert -- (50° C) --; and at line 9, delete "magnesiun" and insert -- magnesium --.

The requested corrections are for typographical errors that appear to have been made by the Patent Office. Therefore, no fee is believed to be due for this request. Should any fees be required, however, please charge such fees to Winston & Strawn LLP Deposit Account No. 50-1814. Please issue a Certificate of Correction in due course.

Respectfully submitted,

2/25/05
Date

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

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DATED: November 16, 2004
INVENTORS: Bologna et al.

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tion of adenyl cyclase by β-adrenergic agonists increases intracellular levels of cAMP. Cyclic AMP in turn reduces the availability of intracellular free Ca^{2+}, which is required for the activation of myosin light-chain kinase, the enzyme that phosphorylates myosin and thereby allows it to combine with actin to form actomyosin. Lack of Ca^{2+} results in disruption of the actin-myosin interaction, with resultant inhibition of smooth muscle contractility.

Terbutaline typically is used as a bronchodilator, and has been approved, for example by the United States Food and Drug Administration, for the treatment of asthma. Oral and intravenous terbutaline also have been used as reasonably effective therapies for preterm labor by stopping contractions or postponing delivery. Lyrenas, S., Grahnen, A., Lindberg, B., et. al., *Pharmacokinetics of Terbutaline During Pregnancy, Eur. J. Clin. Pharmacol.,* 29:619–623 (1986); Berg., G., Lindberg C., Ryden G., *Terbutaline in the Treatment of Preterm Labour, Eur. J. Respir. Dis.,* 65:219–230 (1984).

The use of terbutaline in the treatment of dysmenorrhea has been documented. In one study, terbutaline was shown to inhibit myometrial activity, increase blood flow to the uterus, and relieve the pain occurring during uterine contractions accompanying dysmenorrhea. Akerlund, M., Andersson, K. E., and Ingemarsson, E., *Effects of Terbutaline on Myometrial Activity, Uterine Blood Flow, and Lower Abdominal Pain in Women with Primary Dysmenorrhoea, Br. J. of Obstet. & Gyn.,* 83(9): 673–78 (1976). Kullander, S., Svanberg, L., *Terbutaline Inhalation for Alleviation of Severe Pain in Essential Dysmenorrhea, Acta Obstet. Gynecol. Scand.,* 60:425–27 (1981). Although this therapy did provide some efficacy, the treatment was not sufficient for most patients, who had to supplement with other medications for adequate relief. Further, the effect of each spray lasted as little as 1 hour. Id.

Further, using terbutaline and other β-adrenergic agonists for prevention or treatment of dysmenorrhea or premature labor without the normally-expected side effects has been disclosed in Levine, et. al., U.S. Pat. No. 6,126,959. These side effects are discussed further below.

Shortcomings associated with the therapeutic use of β-adrenergic agonists such as terbutaline have limited their utility. For example, they exhibit low bioavailability after oral administration. Although easily absorbed, β-adrenergic agonists exhibit extensive first-pass sulphation. Bioavailability has been estimated at only between 15 and 20%. Concomitant food intake additionally decreases bioavailability by a further 30%. *Bricanyl: Scientific brochure, Astra France Laboratories* (1993).

Additionally, therapeutic uses of terbutaline have produced significant adverse side effects in the patient, as mentioned above, especially with respect to the cardiovascular system. As a sympathomimetic amine, terbutaline can cause problems in patients with cardiovascular disorders, including arrhythmia, coronary insufficiency, and hypertension. Intravenous administration of terbutaline has been associated with palpitations and peripheral tremors. Åkerlund, M., Andersson, K. F., Ingemarsson, I., *Effects of Terbutaline on Myometrial Activity, Uterine Blood Flow and Lower Abdominal Pain in Women With Primary Dysmenorrhea. Br. J. Obstet., Gyncol.,* 83:673–78 (1976). In addition, intravenous terbutaline has been reported to aggravate pre-existing diabetes and ketoacidosis. Terbutaline also may be problematic for patients with hyperthyroidism, diabetes mellitus, or a history of seizures. Other adverse events include tremors, nervousness, increased heart rate, and dizziness. Less frequent adverse effects include headaches, drowsiness, vomiting, nausea, sweating, muscle cramps, and ECG changes. Thus, despite its efficacy, such treatments are often contra-indicated due to the potential adverse consequences—except when administered as discussed in U.S. Pat. No. 6,126,959, cited above.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising of (i) a therapeutically effective amount of a β-adrenergic agonist for the purpose of treating endometriosis or infertility, or for improving fertility; and (ii) a pharmaceutically acceptable bioadhesive carrier.

The present invention also relates to a method of treating endometriosis or infertility, or for improving fertility, comprising administering a therapeutically effective amount of a composition comprising a β-adrenergic agonist and a pharmaceutically acceptable bioadhesive carrier locally to the vaginal mucosa of a patient in need thereof.

The present invention also relates to a method of treating endometriosis or infertility, or for improving fertility, comprising administering a therapeutically effective amount of a composition comprising a β-adrenergic agonist without producing detrimental blood levels of the β-adrenergic agonist.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

"Improving fertility" includes, without limitation, increasing the rate of conception or the fertility in a female subject.

"Therapeutically effective amount" refers to the amount required to produce the desired effect.

"Treating endometriosis" refers to:

(i) preventing endometriosis in a female subject that may be predisposed to endometriosis but have not yet been diagnosed with it;

(ii) inhibiting endometriosis, i.e., arresting its development; and/or

(iii) relieving endometriosis, i.e., causing its regression.

"Treating infertility" includes, without limitation, alleviating infertility, increasing the rate of conception, or improving fertility in a female subject with decreased or impaired fertility or with recognized infertility.

"Patient" refers to a person who is under medical care or treatment.

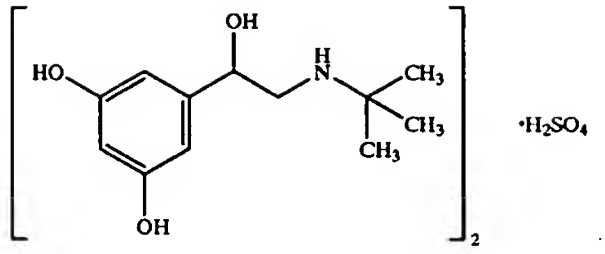
"Vaginal mucosa" refers to the vaginal mucous membrane.

Pharmaceutical Composition of the Present Invention

The present invention relates to a pharmaceutical composition comprising of (i) a therapeutically effective amount of a β-adrenergic agonist for the purpose of treating endometriosis, treating fertility, and/or improving fertility; and (ii) a pharmaceutically acceptable bioadhesive carrier, producing efficacy without detrimental blood levels of the β-adrenergic agonist.

β-adrenergic agonists include, without limitation, terbutaline, ritodrine, isoxsuprine, fenoterol, salbutamol, hexoprenaline, metaproterenol, bitolterol, and pirbuterol.

Preferably, the β-adrenergic agonist is terbutaline. The chemical formula of terbutaline is 5-[2-[(1,1-dimethylethyl) amino]-1-hydroxyethyl]-1,3-benzenediol. Its structural formula is as follows:



The exact mechanism of β-adrenergic agonist's effect on endometriosis, infertility, and fertility is not known, although it is generally thought to act as a uterine smooth muscle relaxant. It is believed that β-adrenergic agonists normalize hyperactive/dyskinetic uterine activity without altering the proper contractile patterns normally occurring during the menstrual cycle. By normalizing dysfunctional uterine contractions, β-adrenergic agonist is expected to decrease pelvic inflammation and pain by decreasing the retrograde bleeding which is thought to contribute to the development of endometriosis. The β-adrenergic agonist's effect on retrograde bleeding can be measured by monitoring levels of CA-125 (Cancer Antigen-125). Normally, CA-125 levels increase during menstruation; however, this increase is even more pronounced in the case of endometriosis. β-adrenergic agonist is believed to reduce the increase in CA-125 levels during menses.

It further is anticipated that β-adrenergic agonists treat infertility associated with endometriosis, even when the visible expression of endometriosis is mild to moderate. Although the exact mechanism of this effect is unknown, it is expected that normalizing retrograde contractions will improve the rapid transport of sperm from the cervical area to the distal end of the tubes where fertilization takes place. Retrograde transport at mid-cycle was evidenced by visualization of retrograde (vaginal to tubal) displacement of Tc-99-labeled macro-albumin aggregates, a technique referred to as hysterosalpingoscintigraphy (HSS).

Additionally, it is expected that β-adrenergic agonists can improve fertility, even in women with no recognized infertility (i.e., women having only a mild degree of uterine dyskinesia, previously recognized or not). Although the exact mechanism of this effect is unknown, in women presenting with uterine dyskinesia, it is believed that terbutaline will improve uterine contractility, thus improving the rapid transport of sperm from the cervical area to the distal end of the tubes where fertilization takes place.

further

It is further expected that any of these indications can be accomplished while avoiding the normally-expected detrimental blood levels of the β-adrenergic agonist.

Further, β-adrenergic agonists offer an advantage over classic treatments of endometriosis in that they do not block ovulation.

A pharmaceutically acceptable bioadhesive carrier is a water-insoluble, water-swellable, bioadhesive cross-linked polycarboxylic acid polymer.

The use of such a polycarboxylic acid polymer bioadhesive carrier in combination with a β-adrenergic agonist offers several advantages over the use of the β-adrenergic agonist alone or with other formulations. Upon administration, such a bioadhesive carrier provides a controlled and prolonged release of a β-adrenergic agonist through the vaginal mucosa. By releasing the β-adrenergic agonist directly and locally through the vaginal mucosa, a relatively reduced but focused concentration of a β-adrenergic agonist is administered. Thus, the systemic concentration of β-adrenergic agonist is reduced, resulting in a decrease in many of the significant side effects associated with first-pass metabolism pathways.

Further, the bioadhesive carrier may be presented in any pharmaceutically acceptable form, including a gel, a cream, a tablet, a pill, a capsule, a suppository, a film, or any other pharmaceutically acceptable form that will adhere to the vaginal mucosa. Because the bioadhesive quality of the present invention prevents the β-adrenergic agonist from being diluted or washed away, the β-adrenergic agonist may be administered effectively, even during menses.

The basic drug delivery system formulation of the present invention—the bioadhesive, water-insoluble water-swellable cross-linked polycarboxylic acid polymer formulation to which is added the β-adrenergic agonist—is generally described in U.S. Pat. No. 4,615,697 to Robinson (hereinafter "the '697 patent"), which is incorporated herein by reference.

At least eighty percent of the monomers of which the polymer is comprised should contain at least one carboxyl functionality. The cross-linking agent must be present at such an amount as to provide sufficient bioadhesion and water insolubility. These characteristics allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place.

This level of bioadhesion is usually attained when the cross-linking agent is present at about 0.1 to 6.0 weight percent of the polymer. More preferably, the cross-linking agent is present at about 1.0 to 2.0 weight percent of the polymer. Suitable cross-linking agents include, among others, divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, and other similar agents. Adhesive strengths may be measured by commercially available surface tensiometers.

A preferred polymer for use herein is Polycarbophil. Polycarbophil U.S.P. is commercially available from B.F. Goodrich Specialty Polymers of Cleveland, Ohio, under the trade name NOVEON®-AA1. Polycarbophil is a polyacrylic acid that is cross-linked with divinyl glycol. *The United States Pharmacopeia*, 1995 edition, United States Pharmacopeial Convention, Inc., Rockville, Md., at pages 1240–41.

Polycarbophil has been used in other drug delivery systems. For example, polycarbophil is a main ingredient in the REPLENS® brand vaginal moisturizer. It has also been used as a base for compositions with other active substances such as progesterone (CRINONE® brand topical progesterone preparation) (see U.S. Pat. No. 5,543,150) and Nonoxynol-9 (ADVANTAGE-S® brand contraceptive gel) (see U.S. Pat. No. 5,667,492).

Other useful bioadhesive polymers that may be used in the inventive composition are mentioned in the '697 patent. For example, these include polyacrylic acid polymers cross-linked with 3,4-dihydroxy-1,5-hexadiene, and polymethacrylic acid polymers cross-linked with divinyl benzene. These polymers should not be used in their salt form because this would decrease their bioadhesive capability. These bioadhesive polymers may be prepared by conventional free radical polymerization techniques known to a skilled artisan, i.e., by utilizing initiators such as benzoyl peroxide and azobisisobutyronitrile. Exemplary methods of preparing useful bioadhesives are also disclosed in the '697 patent.

Additionally, any one or more of the additives taught in the '697 patent may be mixed in with the cross-linked polymer in the formulation for maximum efficacy of the drug delivery system or for the comfort of the patient. Such

ingredient non sensitive to moisture the active is added. The mixture is wet with an aqueous solution of hydroxypropylmethyl cellulose 5 (=HPMC 5) and knead/granulated.

(50°C) The granulate is dried in an oven under warm air (50°C) until moisture content is less than 2.5%

The dried granulate is broken with a stainless steel sieve oscillating granulator mesh size 1000 μm.

magnesium 2. Second step: manufacture of the tableting mixture. Talc, silicon dioxide, magnesiun stearate, and for an active ingredient sensitive to moisture, the active ingredient is added. All are sieved through a sieving machine having an aperture size of 500 μm and then transferred into a free-fall mixer.

Addition of the granulate of step 1, followed by polycarbophil, Carbomer 934P and lactose. The whole is mixed until homogenous.

3. Third step: tableting

The tableting mixture is compressed into tablets by means of a rotative tableting machine equipped with punches 9 mm flat on the upper side and curved (r=9 mm) on the lower side both with beveled edge. The tablets are dedusted and packed.

As described above, an active ingredient that is not sensitive to moisture is preferably added during the manufacture of the granulate. However, alternatively, the active ingredient can be added during the second step after the granulate is dried and sieved. Also, as will be appreciated by one of ordinary skill in the art, this second method is particularly preferred when the active ingredient is sensitive to moisture.

In a presently preferred manufacturing process, the active ingredient is preferably protected from moisture. A wet granulation is made of lactose, corn starch and HPMC. Testosterone, polycarbophil, Carbomer 934P, talc and magnesium stearate are added dry for the final compression.

Furthermore, as will be appreciated by one of ordinary skill in the art following the teaching of the present application, the materials of construction can be varied to optimize the desired characteristics of the tablet. For example, by progressively decreasing the amount of lactose and corn starch and progressively increasing the amount of Carbomer 934P, the amount of time it takes a tablet to hydrate is progressively increased.

Methods of the Present Invention

The present invention contemplates a method of treating endometriosis, treating fertility, and/or improving fertility comprising administering a therapeutically effective amount of a composition comprising a β-adrenergic agonist and a pharmaceutically acceptable bioadhesive carrier locally to the vaginal mucosa of a patient in need thereof. These methods also can be practiced while avoiding normally-expected detrimental blood levels of the β-adrenergic agonist.

The vaginal route of administration with the specific bioadhesive polymer formulation discussed above is advantageous because it avoids first pass hepatic metabolism, which is typically significant for orally administered β-adrenergic agonists. Recently, this preferential or FIRST UTERINE PASS EFFECT® has been confirmed with [^{3}H] labeled progesterone or terbutaline in an in vitro (ex-vivo) human uterine perfusion model. Therefore, vaginal administration of such a formulation will result in therapeutic concentrations of β-adrenergic agonist in the uterine and systemic concentrations low enough to avoid adverse reactions.

Preferably, about 0.5 g to 2.5 g of the inventive composition is administered vaginally. More preferably, about 1 g to 1.5 g of the composition is administered vaginally.

Further, the amount of β-adrenergic agonist contemplated for the present invention is preferably less than 1 mg to about 8 mg, and more preferably about 2 mg to 4 mg. Dosages of more than 8 mg are generally not recommended due to the side effects accompanying such levels. The composition is administered preferably once every 12 to 96 hours.

For vaginal administration, the inventive composition remains attached to the epithelial surfaces preferably for a period of at least about twenty-four to forty-eight hours. To determine whether the composition remains attached, vaginal pH is measured. Since the inventive composition acts as a buffering agent in a pH range of about 2.5 to about 4.5, pH measurements in this range, and preferably at 4.0 pH, should indicate the continued presence of the inventive composition.

All publications and patent applications mentioned herein are incorporated by reference. Reasonable variations, such as those that would occur to a skilled artisan, can be made herein without departing from the spirit and scope of the invention.

We claim:

1. A method of treating endometriosis, comprising administering a therapeutically effective amount of a composition comprising a β-adrenergic agonist and a pharmaceutically acceptable bioadhesive carrier locally to the vaginal mucosa of a patient in need thereof.

2. The method of claim 1, wherein the β-adrenergic agonist is terbutaline, and the composition is formulated to be administered in a dosage that delivers about 1 mg to about 8 mg of terbutaline.

3. The method of claim 2, wherein the composition is administered in a dosage that delivers about 2 mg to about 4 mg of terbutaline.

4. A method of treating endometriosis, comprising administering a therapeutically effective amount of a composition comprising a β-adrenergic agonist and a pharmaceutically acceptable bioadhesive carrier locally to the vaginal mucosa of a patient in need thereof, while avoiding detrimental blood levels of the β-adrenergic agonist.

5. The method of claim 4, wherein the β-adrenergic agonist is terbutaline.

6. The method of claim 5, wherein the bioadhesive carrier comprises a cross-linked water insoluble but water swellable polycarboxylic acid polymer.

7. The method of claim 6, wherein the polymer is polycarbophil.

8. The method of claim 3, wherein the composition is administered every 12 to 96 hours.

9. The method of claim 3, wherein the composition is administered twice weekly.

10. The method of claim 3, wherein the composition is administered in the form of a tablet.

11. The method of claim 3, wherein the composition is administered in the form of a gel or cream.

12. A method of treating infertility, or of improving fertility, by inhibiting retrograde contractions or by improving uterine contractility, comprising administering a therapeutically effective amount of a composition comprising a β-adrenergic agonist and a pharmaceutically acceptable bioadhesive carrier locally to the vaginal mucosa of a patient in need thereof, wherein the amount administered is sufficient to inhibit retrograde contractions or improve uterine contractility.

13. The method of claim 12, wherein the β-adrenergic agonist is terbutaline.

14. The method of claim 13, wherein the composition is formulated to be administered in a dosage that delivers about 1 mg to about 8 mg of terbutaline.